REVIEW ARTICLE

Overview of Cancer and Medicinal Herbs used for Cancer Therapy

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Abstract

Cancer is a disease in which abnormal cells proliferate in the body. It is a group of various diseases involving uncontrolled multiplication and division of abnormal cells in the body. These abnormal cells form malignant growths which called neoplasm. Nowadays, cancer considered as one of the most prevalent diseases in the world, and its mortality is increasing. It is necessary to investigate new strategies to prevent and treat disease. Herbal medicines block critical biochemical pathways converting normal cells to cancer cells for treatment. Herbal medicines block signal transduction in cancer which is a primary channel, by such as controlling nuclear factor-kB signaling pathway, protein tyrosine kinase pathway, and mitogen-activated protein kinases signal pathways. The various study reported that people with cancer commonly use herbal products because of no side effects on healthy cells. Herbal medicine is one of the most widely used alternative therapies by people with cancer. Clinically proven herbal remedies help to prevent or relieve the symptoms of cancer or treatment side effects by a conventional method. We have discussed various medicinal herbs found in India which have the potential to be used in cancer therapy. This present review will focus on the different medicinal plants containing chemical constituents used in the treatment of cancer with their possible mechanism of action.

Key words: Anticancer compounds, cancer, herbal-drug interactions, medicinal herbs

INTRODUCTION

The disease was first named cancer by the Greek physician Hippocrates, Father of Medicine, who applied Greek words "carcinoma" and "Karakinos" to describe a tumor.[1] Cancers are a family of diseases that involve abnormal growth of the cells which spreads to other parts of the body.[2] Cancer was named about the type of tissue from which they arise.[3] Tumors resulting from epithelia are called "carcinomas." In both genders, cancers of the lung, colon, and rectum are the most significant problem. Breast cancer is common in women and prostate cancer in men. Breast cancers are not quite as prevalent as these "major four" diseases. They include carcinomas of the bladder, stomach, liver, kidney, pancreas, esophagus, and cervix and ovary in women. Epidemiology of cancers is most natural skin cancer. They are rarely deadly, with the important exception of melanoma. Testicular cancer is the most frequent cancer affecting young adult males.[4]

Unfortunately, neither incidence nor mortality of human cancer has been much depreciating by conscious human intervention over the past years. Surgery and radiotherapy are a successful treatment in many cases, and chemotherapy is moderately efficacious for some advanced cancers. In general, a modification made in cure and survival rates for these. Modern cancer therapy identifies that not presently available treatments can cure every malignant tumor. Hence, treatment needs to be carefully chosen to maximize the chance for a cure while retaining a maximum of life quality. Significant steps toward successful treatment were made with specific cancers. Those modifications had a small effect on the impact of cancer on the overall population but have helped many individuals, often young people and children. Hence, better knowledge of the molecular and cellular basis will eventually open the door to successful treatment of the primary carcinomas, as will the development of new drugs and new therapies based on the results of molecular biological cancer research.[4]

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CAUSES OF CANCER

The majority of cancers are due to environmental factors. The main reason of cancer are related to the environmental, lifestyle or behavioural exposures. The ecological factors that contribute to cancer death include chemicals in tobacco smoke, radiation, such as ultraviolet rays from the sun, obesity, stress, lack of exercise and environmental pollutants. Exposure to substances linked to specific types of cancer such as exogenous chemical, physical, or natural carcinogens.[5]

CLASSIFICATION OF HUMAN CARCINOGEN

a. Chemical carcinogens: Nickel, cadmium, arsenic, nitrosamines, trichloroethylene, arylamines, benzopyrene, aflatoxins, and reactive oxygen species.
b. Physical carcinogens: Ultraviolet irradiation (specifically UVB), ionizing radiation.
c. Biological carcinogens: Human papillomavirus, Epstein–Barr Virus, hepatitis virus B, *Helicobacter pylori*, etc.
d. Endogenous processes: DNA replication, metabolic reactions, and chronic inflammation.

CANCER BY GENETIC CHANGES

Changes in genes cause disease. The mutation in the different types of a gene often are associated with different forms of cancer. These altered or mutated genes can be broadly classified into three groups, such as proto-oncogenes, tumor suppressor genes, and DNA repair genes.
Proto-oncogenes:

1. These genes involved in healthy cell growth and division. Alteration in these genes may become cancer-causing genes.
2. Tumor suppressor genes involved in controlling cell growth and division.
3. DNA repair genes participate in repairing damaged DNA. Mutation in these genes develops additional variation in other genes. These mutations may cause the cells become cancerous.[5,6]

CHARACTERISTICS OF CANCER AND CANCER CELLS

Human diseases share several essential features:

- Increased cell proliferation (often autonomous)
- Insufficient apoptosis
- Altered cell and tissue differentiation
- Altered metabolism
- Genomic instability
- Immortalization (growth beyond replicative senectitude)
- Conquering into different tissue layers and other tissues
- Metastasis to local lymph nodes and distant tissues.[6]

CLASSIFICATION OF CANCER

Cancer is classified regarding the site of origin of the malignant cells; the histology or cell lysis (called grading); and the extent of disease (called staging).[7]

Site of cancer origin

This classification describes the tissues in which the cancer cells begin to develop. Following are the examples of the location of tumorgenesis categorization.

- Adenocarcinoma (prostate cancer) - originates in gland cells.
- Blastoma (embryonal carcinosarcoma) - arises in fetal tissues.
- Carcinoma (cancer) - originates in epithelial tissue.
- Myeloblastic Leukemia - occurs in tissues which generate cells of blood.
- Lymphoma (malignant neoplastic disease) - occurs in tissue.
- Myeloma - a tumor of the bone marrow composed of cells normally found in bone marrow.
- Sarcoma - originates in connective tissue such as bone, cartilage, and muscle.[7]

Grading

The degree of malignancy of a tumor is estimated by grading systems. The abnormal behavior of the cells determines the grade of cancer. Increasing abnormality of cells increases the degree, from 1 to 4. The most general scheme is G grading, which ranks from G0 to G4.

- G0 denotes normal differentiation and no cellular atypia.
- G4 denotes cellular morphology entirely different from the normal tissue.
- G1, G2, and G3 grades are defined well-differentiated, moderately and poorly differentiated.[7]

Histological classification

Cancer is classified histologically by the location of the tumor. Histological typing of tumors performed by evaluating their morphology. A tumor is histologically classified from surgical specimens. Biological markers improved tumor classification by histopathological classification. For hematological classification, genetic science techniques are used.[8]

Staging classification

The extension of a tumor is defined by "staging."

Two types of stages were described as follows:
Clinical stage:

1. Before surgery, a clinical stage is defined by visual examination, pulsation, and various imaging techniques. These methods use ultrasound, X-rays, computed tomography, and magnetic resonance. "c" prefix denotes it.

Pathological stage:

2. After surgery performed, a more precise examination of the tumor can be made by inspection of the tumor site and by histopathological investigation of the specimen. The stage defined pathological stages, and "p" prefix denotes it.

Mostly used and systematic staging system is the tumor, node, and metastasis system.

Cancer is classified by tumor size (T), the degree of node development (N), and distant metastasis (M), while others remain in use for specific cancers.[8]

CANCER TREATMENT

Methods of cancer treatment

Surgery and chemotherapy are considered as the most common methods of cancer treatment; these methods have severe side effects in use.[3] One of the biggest problems in cancer treatment is gradually increasing the resistance of cancer cells against treatment.[9] Therefore, developing a new approach is one of the primary objectives of immunopharmacological studies to improve cancer treatment results.[10] Nowadays, herbal medicines have played a significant role in controlling cancer symptoms and treatments with minimizing side effects.[11] Some medicinal herbs induce apoptotic pathways through various mechanisms in cancer cells. Medicinal plant constituents include vinca alkaloids (vinblastine and vincristine), taxanes (paclitaxel and docetaxel), podophyllotoxin, and its derivatives (topotecan and irinotecan). Camptothecins have clinically used as plant-derived anticancer agents.[12,13] A list of marketed anticancer herbal medicines are given in Table 1.

Herbal medicines in cancer treatment

In India, herbal medicines have been used for centuries to treat many different health problems. It includes plants or mixture of plant extracts to treat illness and promote health. Herbal medicines are one of the most generally used complementary and alternative methods by people with cancer.[14]

Medicinal plants with anticancer activity

Cassia fistula

It is a plant also known as the golden shower in the family *Fabaceae*. *C. fistula* had many medicinal properties such as purgative and laxative and was used for various disorders such as hematemesis, pruritus, leukoderma, and diabetes.[15,16] *C. fistula* is a primary source of naturally occurring bioactive compounds. Bioactive compound polyphenolics present in this plant proved to be important, non-toxic chemopreventive agents against various oxidative stresses in both *in vitr*o and *in vivo*.[17,18]

Terminalia arjuna

It is a tree of genus *Terminalia* representing a substantial tropical component of the family *Combretaceae* also known as *arjuna*. Various *Terminalia* species had used in traditional treatments of cancer. Photochemical luteolin, gallic acid, and ethyl ester in *T. arjuna* provide scientific evidence supporting the traditional medical application of extracts of this tree in cancer treatments.[19]

Cissus quadrangularis

It is a medicinal plant belonged to family *Vitaceae*[20] and known as asthisamhara in Sanskrit, meaning "which will strengthen the bones." The plant contains significant amounts of Vitamin C, carotene, anabolic steroid substances, and column.[20] It is used as an antioxidant in many applications.

Psoralea corylifolia

The seeds of *P. corylifolia* had used as an ancient Hindu remedy for leukoderma which belongs to family *Fabaceae*.[21] The furanocoumarin psoralen from *P. corylifolia* seeds has been shown to be active against cutaneous T-cell lymphoma and cytotoxic *in vitro* to cultured mucoepidermoid carcinoma cells of MEC-1 cell line.[22,23] *P. corylifolia* seed extract PCSE possesses an immunomodulatory activity and increases in the cell-mediated and humoral immune responses.

Eclipta Alba

E. alba is called Bhringaraja, considered a primary liver herb in Ayurveda.[24] Hydroalcoholic extract of *E. alba* was shown to possess antiproliferative, apoptotic, and anti-invasive activities.[24,25]

Gymnema Sylvestre

G. sylvestre is a plant that found in the forests of India.[26] Five water-soluble polysaccharides (GSP11, GSP22, GSP33, GSP44, and GSP55) were obtained from *G. sylvestre*[26] having the potential of natural antitumor agents.

Table 1: List of marketed anticancer herbal medicines

Class	Drugs	Plant source
Vinca alkaloids	Vincristine Vinblastine	*Catharanthus roseus* (Apocynaceae)
Taxanes	Paclitaxel Docetaxel	*Taxus brevifolia* (Taxaceae)
Epipodophyllotoxin	Etoposide	*Podophyllum hexandrum* (Berberidaceae)
Camptothecin analogs	Topotecan Irinotecan	*Camptotheca acuminata* (Nyssaceae)
Colchicine	Demecoline	Cocus *Colchicum autumnale* (Liliaceae)
Maytansinoid	Mcytanacine Maytansine	*Maytenus buchananii,* *Morus serrata* (Celastraceae)
Macrocyclic lactones	Bryostatins	Bryozoa *Bugula neritina*
Quassinoids	Bruceantin brusato	*Brucea javanica* (Simaroubaceae)
Curcuma	Curcumin	*Curcuma longa* (Zingiberaceae)
Flavonoids	Vicenin Orentin	*Ocimum sanctum* (Labiatae)
Sesquiterpene	Gossypol	*Gossypium barbadense* (Gossypiaceae)
Ellipticine	Ellipticine	*Ochrosia elliptica* (Apocynaceae)
Phthalide isoquinoline alkaloid	Noscapine	*Papaver somniferum* (Papaveraceae)
Acetogenins	Acetogenin	*Annona* species (Annonaceae)

Tinospora cordifolia

This plant used in many drug preparation for general health and disease condition belongs to family *Menispermaceae*. Its stem extracts showed phagocytic and reduced solid tumor volume and successfully employed in many preparations with immune stimulating activity.[27]

Curcuma aromatica

C. aromatica having Curcuma genus belongs to family *Zingiberaceae* has identified as having anti-inflammatory, anti-oxidative stress, and anticancer properties.[28,29] The main biological active components of *C. aromatic* which mainly contains curcuminoids: Curcumin, bisdemethoxycurcumin, and desmethoxycurcumin and sesquiterpenoids including turmerone, germacrene, and β-elemene which were used for cancer treatment.[28]

Symplocos racemosa

S. racemosa belonging to a family (*Symplocaceae*) is a traditional Ayurvedic medicine. The general names of *S. racemosa* are astringent bark, Lodha, Godhra, rodhra, and lodhraka.[29] The study reported the vital ingredients such as phenol, flavonoids, triterpenoids, steroids, tannins, lignans, and coumarins which are responsible for the anticancer activity of the plant extract.[30,31]

Capsicum annuum

C. annuum is widely used as vegetables and food colorants which are a good source of carotenoid pigments.[32,33] The red carotenoids in paprika (*C. annuum* L.) are mainly capsanthin, capsorubin, and capsanthin 3,6-epoxide in which capsanthin and capsorubin have been reported to show antioxidative activities.[34,35]

Mesua ferrea

M. ferrea known as "Nagakesara"[36] reported for antioxidant,[37,38] hepatoprotective,[39] analgesic,[40] antimicrobial,[41] antivenom,[42] anticancer,[43] antiulcer,[44] anti-inflammatory,[45] antiasthmatic,[46] and other several activities. The study reported that the mixture of isolated compounds, α-amyrin or β-amyrin and lupeol were isolated from the dichloromethane extract of *M. ferrea* stems exhibited anticancer activity against MCF-7, KB and NCI-H187 cancer cell lines.[47,48]

Boerhavia diffusa

B. diffusa Linn (Punarnava; family *Nyctaginaceae*) is an abundant creeper found all over India. Extract of *B. diffusa* inhibited the proliferation of various cell lines of human and mouse origin and had significant antiproliferative action in T-cell mitogen (PHA as well as Con A) and antigen (purified protein

derivative)-stimulated human peripheral blood mononuclear cell and immunosuppressive/antiproliferative activity.[49,50]

Terminalia bellerica

T. bellerica known as belleric myrobalan belongs to family *Combretaceae*, found in grasslands and hills of Southeast Asia. This plant extract having several pharmacological effects including antibacterial, antimalarial, antifungal, anti-HIV, antioxidant, and antimutagenic effects[50-53] reported anti-proliferative effects in cancer cell lines including breast cancer MCF-7, prostate cancer PC-3, and DU-145 cells.[54] *T. bellerica* contains chemical components, including gallic acid.[55,56] which has been shown to induce apoptotic cell death in cancer cells.[57-59]

MECHANISM OF HERBAL MEDICINE FOR TREATMENT OF CANCER

Medicinal herbs act through various mechanisms.

Disruption in cell signal transduction pathways

Cancer is strongly associated with defects in signal-transduction proteins which results in uncontrolled or inappropriate cell growth. Herbal drugs block signal transduction in cancer by various routes as following.

Nuclear factor (NF-kB) pathways with activator protein (Ap-1)

Nuclear factor (NF-kB) with activator protein-1 (AP-1) are transcription factors regulates many gene expression involved in oncogenesis, apoptosis, etc. by extracellular signals. It is mainly a protein complex that regulates transcription of DNA, cytokine production and cell survival. Incorrect regulation of NF-kB associated with cancer, inflammatory and autoimmune diseases.[60] Medicinal herbs inhibit the growth of cancer cells by this mechanism, like botanical extract of mountain ginseng inhibits the growth of lung cancer cells through regulating NF-kB signaling pathway.[60]

Protein tyrosine kinase (PTK) pathways

It is a type of enzyme that can transfer a phosphate group to a protein in the cell. Hence, it is called PTK. It functions as an active and not active in many cellular reactions. It causes growth in signal transduction to cells.[61]

Modification in cycle of cell

The natural and constant balance of cycle of cell ensures standard cell escalation. The change in cell cycle concludes the tumor. Elongation of the cell cycle caused by the existence in the control points in G1 and G2 phases. Neoplastic cells are not capable of preventing cell division at the control points (G1/S and G2/M), and proliferation of cells becomes deregulated.[61]

Mitogen-activated protein kinases (MAPK) signal pathways

MAPK signaling pathway induces signals for the division of cells. Hence, carcinogenesis caused by deregulation of MAPK signal pathways.[60] Such technique is applied to induce apoptosis.[62]

Cyclooxygenase (Cox-2) pathways

Cyclooxygenase is known as a Cox-2 inhibitor which catalyzed the prostaglandin synthesis. Inhibition of COx-2 affects the growth of tumor cells through inhibiting cell proliferation.[63]

Intervention with microscopically small tubules

Microscopically small tubules are known as microtubules present in the cytoplasm of cells. Microtubules play a vital role in preventing alignment of the daughter chromosomes and consequently stop of mitosis at anaphase, which finally followed by apoptosis.[1] It was reported that herbaceous plant phytochemicals such as vinca alkaloids (vincristine and vinblastine) and taxanes are important microtubulin-binding factors.

Topoisomerase inhibitor

Herbal drugs are having a crucial role in cancer treatment with balancing capacity of topoisomerases. Camptothecins inhibit topoisomerase-I, and epipodophyllotoxins inhibit topoisomerase II.[1]

SAFETY AND PHARMACEUTICAL INTERACTIONS OF HERBAL MEDICINES

Security is defined as a condition in which a substance or a drug is targeted to be safe or dangerous and showing potent effects against long-term and short-term side effects. Since herbal products used plants, extracts, and mixtures which are natural, so they were often safe for treatment. However, in some cases, different adverse effects were reported by administration of some herbal medicines through various mechanisms such as direct toxicity of plant, allergy, plant pollutants like lead, mercury, arsenic, and pharmaceutical interactions with other medications.[64]

Herbal-drug interactions were particularly pertinent in such cases like when cardiovascular medications such as

digoxin and warfarin with a narrow therapeutic index were administered with herbal drugs that can potentiate or reduce pharmacologic effects of medicine.[3,60] Thus, an appropriate counseling has been done by health-care professionals to patients about use of herbal drugs. For this purpose, adequately designed clinical trials are conducted to assess the safety and efficacy of herbal medicine, like the possible interaction with medications.

HERBAL MEDICINES AND CHEMICAL DRUG INTERACTIONS

Two types of interactions are shown with the administration of herbal medicine and chemical drugs.

Pharmacodynamic interaction

Pharmacodynamic interactions defined as a drug or herbal product affect a tissue or organ. This type of interactions affects the activity of medicine such as an increase (synergistic property) or decrease (antagonizing property) in drug effect. For example, genistein used in human prostate adenocarcinoma PC3 cells with combination usage of β-lapachone-genistein-induced apoptosis is more officious. Valerian is a herbal compound used as a painkiller was reported to decrease with the administration of benzodiazepine.[60,65,66]

Pharmacokinetic interaction

Pharmacokinetics effects such as absorption, dissemination, metabolism, secretion, and toxicity of administered medicines affected by herbal medicines. Such type of communications has especially shown when herbal constituents affect hepatic enzymes[67] like interactions between ginseng and warfarin. Ginseng reduced anticoagulation effects of warfarin plasma level reduced.[68,69] Even though most people believe that natural treatments are safe inherently, herbal medicine may cause some dangers.[65]

CONCLUSION AND FUTURE ASPECTS

In this review, we have come to the conclusion that many natural medicinal herbs can be used as effective medicines for cancer treatment. We have found that many herbaceous plants for cancer treatments, but there had been not enough research. Replacement of herbal medicine is not possible, but it can be used for cancer treatment. Using herbal medicines, we can overcome the side effects of the conventional method of cancer treatment such as radiotherapy and chemotherapy. Examining the fact that little was known about efficacy, safety, and use of herbal products, and not paying attention, further research can improve appropriate use of plants in cancer treatment.

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